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TITLE: Phase 2 Clinical Trial of AC105 (Mg/PEG) for Treatment of Acute Spinal Cord Injury (SCI)

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**14. ABSTRACT**

Research has shown that tissue magnesium (Mg) is rapidly depleted in injured central nervous system (CNS), and this depletion correlates with the severity of injury in animal models (Heath and Vink, 1999). Exogenously delivered Mg reduces injury in animals (Kwon et al., 2009) but conventional systemic Mg therapy is limited by the inability to achieve sufficient CNS levels to be effectively neuroprotective. AC105 is a polyethylene glycol (PEG) formulation of Mg that was shown to more effectively deliver Mg to the injured CNS. The primary hypothesis of this study was that treatment of people with acute spinal cord injury (SCI) with the polymer formulation of magnesium known as AC-105 would result in greater normalization of CNS Mg than treatment with saline solutions and potentially improve neurological outcome from injury. This was a Phase 2 double-blind, placebo-controlled study to determine the safety, tolerability and potential activity of AC105 following a regimen of 6 doses over 30 hours in patients with acute SCI. Forty (40) subjects were planned for enrollment into one of the two treatment groups, AC105 or placebo, randomized in a 1:1 allocation. The study was terminated by the Sponsor due to an insufficient rate of enrollment and patient retention: at the time of study termination, a total of 15 subjects had been enrolled.

**15. SUBJECT TERMS**

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## Contents

## INTRODUCTION

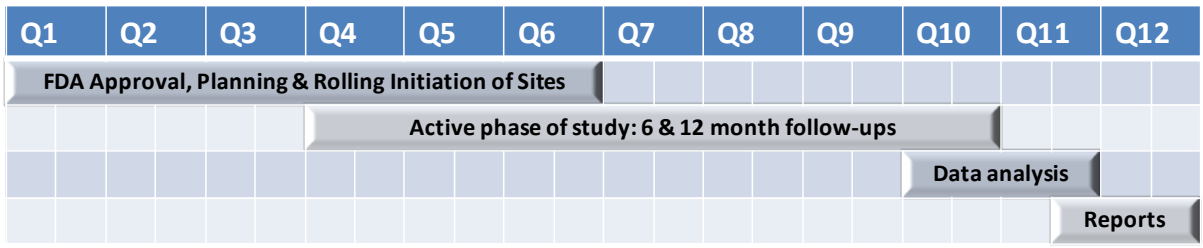
At the time of this study, Acorda Therapeutics was developing AC105 for the treatment of acute spinal cord injury. Research has shown that tissue magnesium (Mg) is rapidly depleted in injured central nervous system (CNS), and this depletion correlates with the severity of injury in animal models (Heath and Vink, 1999). Exogenously delivered Mg reduces injury in animals (Kwon et al., 2009) but conventional systemic Mg therapy is limited by the inability to achieve sufficient CNS levels to be effectively neuroprotective. AC105 is a polyethylene glycol (PEG) formulation of Mg that was shown to more effectively deliver Mg to the injured CNS. The primary hypothesis of this study was that treatment of people with acute spinal cord injury (SCI) with the polymer formulation of magnesium known as AC-105 would result in greater normalization of CNS Mg than treatment with saline solutions and potentially improve neurological outcome from injury. This was a Phase 2 double-blind, placebo-controlled study to determine the safety, tolerability and potential activity of AC105 following a regimen of 6 doses over 30 hours in patients with acute SCI. Forty (40) subjects were planned for enrollment into one of the two treatment groups, AC105 or placebo, randomized in a 1:1 allocation. The study was terminated by the Sponsor due to an insufficient rate of enrollment and patient retention: at the time of study termination, a total of 15 subjects had been enrolled.

## KEY RESEARCH ACCOMPLISHMENTS

The Specific Aims of the project were:

1. To complete a Phase 2, double-blind, randomized, placebo-controlled study of AC-105 by intravenous infusion in patients with acute SCI, treated as soon as possible following injury beginning with a treatment window of up to 12 hours and subsequently restricting this to 9, then 6 hours post-injury.
2. To examine potential effects of AC-105 on changes in potential biomarkers of CNS tissue damage after spinal cord injury.
3. To compare the neurological outcome from injury at specific time-points after injury through 6 months for the randomized groups treated with AC-105 and placebo.
4. To determine the feasibility of a large Phase 3 study to determine the efficacy of AC-105 in acute SCI using clinically meaningful outcome measures that could be agreed to with the Food and Drug Administration (FDA).

At least twenty patients were to be randomized per group (40 total). With an estimated average recruitment of 1 patient every 3 months at each center, a staged initiation of 10 centers in the first 6 months, and an additional 10 centers over the next 6 months, the subject recruitment phase would have required approximately 1 year. The follow-up phase would have required an additional year from the last patient recruited. Approximately 3 months would have been required for data cleaning and analysis and a final 3 months for assembly of the study reports (clinical and biomarker study reports).




The Proposed Milestones for the project were:

1. Month 3 – FDA approval of clinical protocol
2. Month 6 – First site initiation and IRB approval, Investigator Meeting completed
3. Month 9 – First 5 sites initiated
4. Month 12 – Initiation of first 10 sites completed
5. Month 18 – Initiation of all 20 sites completed, enrollment of all 40 patients completed
6. Month 27 – Last patient completes 6 month follow-up
7. Month 30 – Database lock for analysis of 6 month data
8. Month 33 – Final reports on clinical study and biomarker investigation completed
9. Month 36 – Addendum report on 12 month follow-up data completed

- Study ACPM-SI-1009 Protocol version 1.0 completed 23 August 2012. This was subsequently amended (14 December 2012, version 2.0) primarily to restrict the age of participants to 18-65.
- An Investigator Meeting was held 10-11 May 2013, Chicago, IL.
- 21 clinical investigative sites in the United States and Canada were initiated and activated. Only seven of those sites eventually enrolled patients.
- No Object Letter (NOL) received from Health Canada on November 21, 2013 with request to revise ICF. ICF version 5.0 (December 4, 2013) per Health Canada's request sent to the sites. The ICF was revised per the request of Health Canada and contains clarification on the potential risk to women who may be pregnant (and to the unborn child) after receiving the first dose of study treatment.
- A Protocol amendment (v3.0) (10 September 2013) and ICF amendment (v4.0, 24 October 2013) were sent to sites, FDA and Health Canada. Sites received training on the protocol amendment, which primarily was changed to allow further restriction of the time window of treatment, first to 9 hours and then to 6 hours post injury.
- The Pharmacy Manual Version 4.0 dated 26 February 2014 was updated to reflect the changes in Protocol Amendment Version 3.0. Site pharmacists received pharmacy training.
- An Investigators Teleconference was held on 19 March 2014 to provide a study update and share experiences on enrolling patients from those few sites that had been able to do so. Only six patients were actively enrolled at that time.
- The first Data Safety Monitoring Board (DSMB) Meeting to review data was held 23 April 2014. The DSMB recommendation was to continue enrollment. No significant safety issues were identified that were out of the known natural history of SCI. The second DSMB meeting was held on 30 October 2014 and a copy of the DSMB Safety

Recommendation form was submitted to HRPO. The last DSMB meeting was held in May 2015.

- Eleven (11) Serious Adverse Events (SAEs) were reported and submitted to HRPO. No IND safety reports were issued.
- Based on the low rate of enrollment and the number of discontinuations from the study, Acorda decided in November 2014 to stop further enrollment and terminate the study when all currently enrolled subjects complete the follow-up visit. The last subject follow-up visit occurred in February 2015.
- Inactive sites were closed immediately. Active sites with enrolled subjects were closed when last subject last visit was completed. IRBs notified of study close out. IRB closeout notifications submitted to HRPO.
- Database lock was completed May 2015.
- The Trial Master File was transferred from the CRO to Acorda in October 2015.
- An abbreviated Clinical Study Report (CSR) was completed in November 2015.

The overall disposition of patients is shown in the Table 4 from the abbreviated clinical study report, reproduced below:

**Table 4: Subject Disposition by Treatment Group**

| | Placebo | AC105 | Total |
|---|---|---|---|
| **Screen Failure** | -- | -- | 5 |
| **Subjects Randomized** | 8 | 7 | 15 |
| **Safety Population*** | 6 (75.0%) | 7 (100.0%) | 13 (86.7%) |
| **Subjects that Completed Study**** | 4 (66.7%) | 5 (71.4%) | 9 (69.2%) |
| **Subjects that Discontinued Study**** | 2 (33.3%) | 2 (28.6%) | 4 (30.8%) |
| **Primary Reason for Discontinuation**** | | | |
| Death | 1 (16.7%) | 0 (0.0%) | 1 (7.7%) |
| Non-compliance with Study Drug | 0 (0.0%) | 1 (14.3%) | 1 (7.7%) |
| Other*** | 0 (0.0%) | 1 (14.3%) | 1 (7.7%) |
| Protocol Violation | 1 (16.7%) | 0 (0.0%) | 1 (7.7%) |

*: Percentages are based on the number of randomized subjects in each column.
**: Percentages are based on the number of subjects in the Safety Population in each column.
***: Subject 101002 was unable to complete the Month 6 Visit and was withdrawn by the Sponsor (see Listing 16.2.1.1)
Reference: Table 14.1.1

This study was not designed to promote or create professional development. Additionally study results and data were not disseminated to the public or to communities of interest. As this is the Final Report, no additional reporting periods are planned.

## CONCLUSIONS

The primary impact of this study was the identification of significant challenges to conducting a multicenter trial in acute spinal cord injury that involves rapid initiation of treatment, i.e. treatment begun within a few hours of injury. Investigators were able to recruit patients, albeit slowly, with a treatment window of 12 hours. With the treatment window reduced to 9 hours the recruitment rate was quite impractical. This is an important observation for the field.

As this study was terminated after enrolling 15 of 40 planned patients, no meaningful assessment could be attempted of the potential impact of AC105 relative to saline on lesion volume or clinical outcome.

The study was terminated by the Sponsor due to an insufficient rate of enrollment combined with a relatively high rate of discontinuation. A total of 15 subjects were enrolled at 7 centers in the US. Of those enrolled, 2 subjects (Subjects 102003 and 109001) randomized to placebo were subsequently deemed ineligible and were not treated with the investigational product; they were excluded from the analysis. This smaller number of subjects (7 receiving AC105 and 8 receiving placebo) was further reduced to only 5 subjects receiving AC105 and 3 receiving Placebo who had both a baseline and follow-up MRI scans that were centrally read for change in SCI status at 6 months follow up compared to baseline (called global review).

**Adverse Events**

A total of 13 subjects received at least one infusion of investigational product (AC105 or placebo) and were included in the Safety Population: 7 in the AC105 treatment group and 6 in the placebo group. Four subjects discontinued from the study, of which one was due to death (respiratory failure). (Subject 113002, randomized to placebo).

Of the 13 subjects included in the safety analysis, 10 subjects reported Treatment Emergent Adverse Events (TEAEs). The percentages of subjects experiencing TEAEs characterized as mild, moderate, and severe severity were 76.9%, 61.5%, and 38.5%, respectively. In the AC105 arm, 6 of 7 patients reported one or more TEAEs compared with 4 of 6 patients in the placebo arm. Two subjects reported TEAEs that were considered possibly related to the investigational product by the investigator (both in the AC105 group):

**Subject 102004**, randomized to AC105, reported a mild TEAE of Nausea, which began approximately 2 hours after the start of treatment with the investigational product; the subject received additional treatment and recovered from the nausea.

**Subject 127004**, randomized to AC105, reported a mild TEAE of Hypertension, which began approximately 30 minutes after the start of treatment with the investigational product; no action was taken and the subject recovered from the hypertension.

All other TEAEs in the study were considered unlikely related or unrelated to the investigation product by the investigator.

The most common TEAE (> 20%) in the AC105 treatment group were nausea, anxiety, pneumonia, depression, hypotension, neuralgia, urinary tract infection, ileus, insomnia, oxygen saturation decreased, and pulmonary embolism. The number of patients in the study was too small to interpret the incidence of these events in the two groups.

Additionally, 3 subjects experienced serious TEAEs during the study; the events were considered unrelated or unlikely related to the investigational product by the investigator. One subject randomized to the placebo group died due to a TEAE (respiratory failure) deemed unrelated to the investigational product by the investigator.

**Subject 113002**, randomized to placebo, experienced a moderate treatment-emergent adverse event (TEAE) of Wound Dehiscence, a severe TEAE of Respiratory Failure, as well as a severe and serious TEAE of Respiratory Arrest, resulting in death. All 3 events were considered not related to the investigational product by the investigator and events not unusual to the underlying condition of acute spinal cord injury.

**Subject 113003**, randomized to AC105, reported a severe TEAE of Pneumonia; the event was considered not related to the investigational product by the investigator.

**Subject 127004**, randomized to AC105, reported a moderate TEAE of Pleural Effusion and a mild TEAE of Pneumonia. Both events were considered unlikely related to the investigational product by the investigator.

Non-treatment emergent SAEs were reported by 6 subjects.

TEAEs deemed possibly related to the investigational product by the investigator were reported by 2 subjects.

A summary of TEAE is found in Table 6 of the CSR and reproduced below:

**Table 6: Summary of Subjects Reporting Treatment-Emergent Adverse Events by Treatment Administered (Safety Population)**

| | Placebo *(N=6)* | AC105 *(N=7)* | Total *(N=13)* |
|---|---|---|---|
| **Any TEAEs** | 4 (66.7%) | 6 (85.7%) | 10 (76.9%) |
| **Mild TEAEs** | 4 (66.7%) | 6 (85.7%) | 10 (76.9%) |
| **Moderate TEAEs** | 3 (50.0%) | 5 (71.4%) | 8 (61.5%) |
| **Severe TEAEs** | 2 (33.3%) | 3 (42.9%) | 5 (38.5%) |
| **Serious TEAEs** | 1 (16.7%) | 2 (28.6%) | 3 (23.1%) |
| **Drug-related TEAEs*** | 0 (0.0%) | 2 (28.6%) | 2 (15.4%) |
| **TEAEs leading to death** | 1 (16.7%) | 0 (0.0%) | 1 (7.7%) |
| **TEAE leading to discontinuation** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

* AEs considered related or possibly related to the investigational product by the investigator

Overall, a higher proportion of subjects treated with AC105 reported adverse events in this study. However, the high number of adverse events considered not related or unlikely related to the investigational product suggests that the underlying SCI and the subsequent medical management of subjects should be considered in the interpretation of safety findings. Due to low recruitment, small sample size in both study arms, as well as confounding factors related to the baseline disposition of subjects, further investigation is necessary to determine the impact of AC105 on the safety of this patient population.

**Changes in the Conduct of the Study**

The following is a list of protocol amendments during the study:

Protocol version 1.0, released on 23 August 2012

Major changes from V1.0 to V2.0:

- For clearer understanding study results, it was deemed appropriate to exclude patients who received magnesium prior to the study.
- As a condition of receipt of grant from the DoD, no minors are to be enrolled in this study.
- Added early termination procedures and criteria for patient replacement—advertently omitted in previous version.
- To specify the parameters that will be tested, at minimum, and provide clarity on Mg testing.
- The Spinal Cord Independence Measure (SCIM III assessment) will be performed at the 3 and 6 month visits. Additional SCIM to provide comparison

- As a condition of receipt of grant from the DoD, the DoD may audit sites per their procedures.

Protocol version 2.0, released on 14 December 2012

Major changes from V2.0 to V3.0:

- Early initiation of treatment after injury is more likely to result in a positive effect on outcome than delayed treatment. Therefore, goal will be to reduce the time to treatment as the study progresses. For this study there will be maximum treatment window of 12 hours post-injury for the first 8 patients who are enrolled and the treatment window will be reduced to 9 hours post-injury for subsequent patients.

- Allows for non-verbal / non-written consent when a patient is conscious and alert but either unable to sign or talk due to the injury and/or interventions.

- In the interests of starting treatment as soon as possible after injury, a urine test which can be evaluated quickly will be used for the initial pregnancy screen. Serum test results which take longer to process will be used for confirmatory testing.

- For safety reason, a patient will be exempted from having an MRI if it is medically contraindicated.

Protocol version 3.0, released on 10 September 2013

## Future Plans

Development of AC-105 by Acorda was terminated based on the lack of feasibility for a Phase 3 program in acute SCI. The rights to the underlying intellectual property were returned to Medtronic Inc., the licensor of the technology.

### Participants & Other Collaborators

Principal Investigator and Participants:

Blight, Andrew PhD (Principal Investigator) No change

Caggiano, Anthony MD, PhD (Co-PI) No change

Carrazana, Enrique MD (Faculty) No change

Rabinowicz, Adrian MD FAAN (Faculty) No change

Marinucci, Lawrence (Faculty) No change

Lammertse, Daniel (Consultant) No change

Kwon, Brian MD (Consultant) No change

Vink, Robert PhD (Consultant) No change

Guest, James MD (Consultant) No change

Brian Walter (Faculty), Bonnie Pappacena (Faculty), Bonnie Faust (Faculty) and Gustavo Suarez (Faculty) are no longer employed at Acorda Therapeutics. Herb Henney (Faculty) now consults for Acorda. Their status change did not impact the study.

The following research sites were initiated during the patient enrollment period of the study:

| Site Number | Site Director | Site Name |
|---|---|---|
| 105 | Arnold, Paul | University of Kansas Hospital, Topeka, KS |
| 103 | Christie, Sean | QEII Health Sciences Center, Halifax, Nova Scotia, Canada |
| 101 | Galler, Robert | Stony Brook Medicine, NY |
| 109 | Harrop, James | Thomas Jefferson University Hospital, Philadelphia, PA |
| 112 | Hsieh, Patrick | University of Southern California, CA |
| 127 | Kang, Matthew | Regions Hospital, MN |
| 102 | Kurpad, Shekar | Medical College of Wisconsin, WI |
| 114 | Kwon, Brian | Vancouver General Hospital, Canada |
| 108 | Ladley, Susan | Denver Health Medical Center, CO |
| 113 | Okonkwo, Davie | University of Pittsburgh, PA |
| 121 | Guest, James | Miami School of Medicine, FL |
| 128 | Shapiro, Scott | Indiana University Health Methodist Hospital, IN |
| 131 | Varelas, Panayiotis | Henry Ford Hospital Neuroscience Institute. MI |
| 118 | Merlotti, Gary | Mt. Sinai Hospital, Chicago, IL |
| *104 | Bockenek, William | Carolinas Rehabilitation, NC |
| *119 | Varma, Abhay | Medical University of South Carolina, SC |
| *120 | Aarabi, Bizhan | University of Maryland , MD |
| *126 | Patterson, Lisa | Baystate Medical Center, MA |
| *117 | Tsai, Eve | The Ottawa Hospital, Canada |
| *129 | Alberico, Anthony | Marshal Health, WV |
| *116 | Surdell, Daniel | University of Nebraska Medical Center, NE |
| *130 | Young, William | Parkview Regional Medical Center, IN |
| *106 | Heary, Robert | New Jersey Medical College, NJ |

*Asterisk (*) indicates a site that was initiated, but terminated due to lack of patient enrollment.*

Additionally, several study sites were selected, but were not initiated. These sites were:

| | | |
|---|---|---|
| 107 | Ahn, Henry | St. Michael's Hospital, Ontario, Canada |
| 110 | Fehlings, Michael | Toronto Western Hospital, Canada |
| 134 | Zacko, Christopher | Penn State Milton S. Hershey Medical Center, PA |
| 132 | Boakye. Maxwell | University of Louisville, KY |

Several sites were selected, but terminated due to lack of patient enrollment.

## APPENDICES

None